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10/715,482	11/19/2003	Naveen Arora	2761-0169P	3751

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
08/09/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/715,482	**Applicant(s)** ARORA ET AL.	
	Examiner Vanessa L. Ford	**Art Unit** 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 July 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *NONE*.
   Claim(s) objected to: *NONE*.
   Claim(s) rejected: *1,3-8,21 and 35-38*.
   Claim(s) withdrawn from consideration: *NONE*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See advisory attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). i
13. ☒ Other: Advisory Attachment.

ROBERT A. ZEMAN
PRIMARY EXAMINER

Advisory Action

1. This action is in response to Applicant's amendment and remarks filed July 7, 2007. It should be noted that in the Final action mailed February 2, 2007 there were typographical errors. The rejection under 35 U.S.C. 112 first paragraph, pages 2-5, paragraph 4, claims 35-38 were invertently omitted. The rejection under 112, first paragraph, pages 5-9, paragraph 5, claims 35-38 were invertently omitted. The rejection under 35 U.S.C. 102(a), pages 9-11, paragraph 6, claims 35-36 and 36 were invertently omitted. The rejection under 35 U.S.C. 102(b), pages 11-12, paragraph 7, claims 35-36 and 36 were invertently omitted. The rejection under 35 U.S.C. 102(b), pages, 12-15, paragraph 8, claims 35-38 were invertently omitted. The rejection under 35 U.S.C. 112 second paragraph, pages 15-16, paragraph 9, claims 35-38 were invertently omitted. The rejection under 35 U.S.C. 112 second paragraph, page 16, paragraph 10, claims 35-38 were invertently omitted. The limitations of the claims 35-38 invertently omitted in the rejections mention above were addressed in the body of the recited rejections. The Office apologizes for the typographical errors.

2. Applicant's amendment is not entered because claim 1 as amended would require further consideration and require new searches because of the newly recited claim limitation "...is isolated from *Imperata cylindrical* and demonstrated that a similar protein is presenting *Lolim perenne, Phleum pretense* and *Cynodon dactylon*".

3. The rejection of claims 1, 3-8, 21 and 35-38 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 2-5, paragraph 4 of the Final Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which lacks written description in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

The claims are directed to a novel protein capable of inhibiting anthrax toxin activity. Dependent claims 2 and 21 recite "... wherein the protein is isolated from pollen grains of a grass of a genus selected from the group consisting of *Imperata,* a genus related to *Imperata*, *Lolium*, a genus related to *Lolium*, *Phleum*, a genus related to *Phleum*, *Cynodon* and a genus related to *Cynodon*" and "...wherein the grass is selected from the group consisting of *Imperata cylindrica, Lolium perenne, Phleum pretense* and *Cynodon datylon*". Therefore, the claims encompass a genus of 67 kDa proteins.

The specification only provides written description for the 67 kDa protein isolated from *Imperata cylindrica.* There is no disclosure that the claimed protein was isolated from a grass other than *Imperata cylindrica.* The instant specification does not describe a 67 kDa protein isolated from pollen grains of a grass of a genus selected from the group consisting of *Imperata,* a genus related to *Imperata*, *Lolium*, a genus related to *Lolcium*, *Phleum*, a genus related to *Phleum*, *Cynodon* and a genus related to *Cynodon*". The specification also fails to provide adequate written description for claimed protein isolated from *Lolium perenne, Phleum pretense* or *Cynodon datylon.*

Bijli et al (*Clin. Exp. Allergy, January 2003, 33:65-71)* teach a 67kDa protein purified from *Imperata cylindrica* (page 65). Verma et al *(International Archives of Allergy and Immunology, 2000, 122:251-256)* teach a 67kDa protein purified from *Imperata cylindrica* that binds IgE (page 252). Therefore, one of skill in the art would not conclude that the claimed novel 67-kda protein could be isolated from a grass other than *Imperata cylindrica.* One skilled in the art would not conclude that Applicant was not in possession of the claimed 67 kDa proteins isolated from the genus of *Lolium, Cynodon* and *Phleum* at the time of filing. Therefore, Applicant has not met the written description requirements as set forth in 35 U.S.C. 112, first paragraph.

Applicant's arguments were addressed in the response to the Final Office action. This rejection is maintained for reasons of record.

4. The rejection of claims 1, 3-8 , 21 and 35-38 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 5-9, paragraph 5 of the Final Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a novel protein capable of inhibiting anthrax toxin activity.

The specification teaches that the protein of the invention can inhibit activity of anthrax toxin (page 2). The specification teaches that the protein has the utility for developing a therapeutic agent that can reduce the toxic effects once the disease has set in (page 2). Therefore the instant specification contemplates the use of the claimed 67 kDa protein to treat anthrax *in vivo*. The claims recites the claim limitation "dose dependent manner" (e.g. claim 1) as well as reciting the specific concentrations of the claimed protein (e.g. claims 5-8). Claim 13 recites the limitation "wherein said protein inhibits anthrax toxin *in vitro*". Thus, the instant specification contemplates *vitro* use. The specification only discloses inhibition studies *in vitro* using claimed 67 kDa protein incubated with J774A.1 (eukaryotic) cells (pages 7-8). The specification has failed to correlate *in vivo* treatment of anthrax using the claimed protein and the *in vitro* treatment of anthrax using the claimed protein. The specification teaches that the novel protein for inhibition of activity of anthrax and the purified protein has the ability or reduce the toxic effects of anthrax (page 2). What toxic effects are reduce? The toxic effects of PA or LF or both or other toxins? What constitutes a reduction? The specification and claims teach that the claimed 67-kDa protein has IgE binding properties. The specification further teaches *in vitro* assays using the claimed protein and *Imperata cylindrica* (Ic) hypersensitive individual's sera, 10 out of 12 sera demonstrated it to be a major allergen (page 6 and Figure 2). Example 7 of the instant specification teaches that the 67 kDa protein was "preincubated" with the J774A.1 cell line in an *in vitro* assay. Therefore, a "preincubation" of the protein with the cells is required. How does this correlate with administering the 67 kDa protein *in vivo*? Will the protein effective *in vivo* if preincubation is not possible? How is the preincubation requirement met *in vivo*? Does the 67 kDa protein reach the reach the target site to inhibit the PA and LF antigens? Verma et al *(International Archives of Allergy and Immunology, 2000, 122:251-256)*

teach that grass pollen allergens have been implicated in the induction of type I allergic disorders in atopic individuals (page 251). Verma et al teach that the 67 kDa protein isolated from *Imperata cylindrica* Pollen Extract showed high IgE binding in ELISA and reacted with 80% of the patients' sera and suggest that the 67 kDa protein may be a new allergen (page 255). Vieths et al *(Ann N.Y. Acad. Sci., 964:47-68, 2002)* teach that pollen-allergic patients frequently present allergic symptoms after ingestion of several kinds of plant-derived food (see the Abstract). Vieths et al teach that approximately 15-20% of the population in developed countries are allergic to pollen and 50-93% of birch pollen-allergic patients have IgE mediated reactions to pollen related foods (page 48). Vieths et al teach that at the molecular level, observations are based on the cross-reactions of human IgE antibodies which are directed against pollen allergens with homologous allergens in plant food (page 48). How would the claimed 67 kDa protein react when administered *in vivo* to patients that produce high levels of IgE neutralizing antibodies due to allergic reactions? Zhao et al *(Human Antibodies, 2003; 12(4):129-35)* teach that neutralizing monoclonal antibodies can block the action of anthrax toxin lethal toxin factor formation (see the Abstract). If neutralizing antibodies are to LF are present, how is the claimed protein when administered *in vivo*? The experimental examples of the instant specification are directed to *in vitro* use. However, the instant specification contemplates both *in vivo* and *in vitro* use of the claimed protein. The instant specification has not presented disclosure that would lead one of skill in the art to conclude that the *in vitro* data present in the specification would correlate with *in vivo* use.

One of skill in the art could have reason to doubt the assertion that the claimed 67 kDa protein would be effective in inhibiting anthrax *in vivo* based on the teachings of the cited art and the absence of evidence in the instant disclosure to correlate inhibition of the anthrax toxins with in vivo administration of the claimed protein.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to using the claimed protein to inhibit the anthrax toxin *in vivo* 3) there are no working examples which suggest the desired results of a successful use of the claimed protein and 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level).

In view of all of the above, it is determined that the specification has not provided guidance that would enable one of skill in the art to be able to use the claimed invention commensurate with the claims. One of skill in the art would require undue experimentation to determine whether the claimed 67 kDa protein can be used to treat or inhibit anthrax toxins *in vivo*.

Applicant's arguments were addressed in the response to the Final Office action. This rejection is maintained for reasons of record.

5. The rejection of claims 1, 3-8, 21, 35-36 and 38 under 35 U.S.C. 102(a) as anticipated by Bijli et al *(Clin. Exp. Allergy, January 2003)* is maintained for the reasons set forth on pages 9-11 paragraph 6 of the Final Office Action.

The rejection was on the grounds that Bijli et al teach a 67kDa protein purified from *Imperata cylindrica* (page 65). Bijli et al teach a protein that is stable at room temperature (see Abstract). Bijli et al teach a 67kDa protein binds IgE (page 68). Claims limitations such as "hydrophobic in nature", "resistant to trypsin", "has no proteolytic activity", "inhibits proteolytic cleavage of protective antigen (PA) of *B. anthracis* in a dose dependent manner", "is devoid of any carbohydrate moiety", "wherein the range of about 25-20 ng completely inhibits the cleavage of the protective antigen of *B. anthracis* by trypsin" wherein protein in the range of about 15-5 ng completely inhibits the cleavage of the protective antigen of *B. anthracis* by trypsin", "wherein the protein in the range of about 25 ng to 11, 000 ng is effective in inhibiting the anthrax activity" and "wherein the protein in the range of about 50 to 10, 000 ng is effective in inhibiting anthrax activity" would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's arguments were addressed in the response to the Final Office action. This rejection is maintained for reasons of record.

6. The rejection of claims 1, 3-8, 21, 35-36 and 38 under 35 U.S.C. 102(b) as anticipated by Bijli et al *(Journal of Immunological Methods 260 (Feb. 2002, 91-96)* is maintained for the reasons set forth on pages 11-12, paragraph 7 of the Final Office Action.

The rejection was on the grounds that Bijli et al teach a 67kDa protein purified from *Imperata cylindrica* that binds IgE (page 93, Figures 1 (a)-(c)). Bijli et al teach a protein that is stable at room temperature (page 92). Claims limitations such as "hydrophobic in nature", "resistant to trypsin", "has no proteolytic activity", "inhibits proteolytic cleavage of protective antigen (PA) of *B. anthracis* in a dose dependent manner" and "is devoid of any carbohydrate moiety", wherein the range of about 25-20 ng completely inhibits the cleavage of the protective antigen of *B. anthracis* by trypsin" "wherein protein in the range of about 15-5 ng completely inhibits the cleavage of the protective antigen of *B. anthracis* by trypsin", "wherein the protein in the range of about 25 ng to 11, 000 ng is effective in inhibiting the anthrax activity" and "wherein the protein in the range of about 50 to 10, 000 ng is effective in inhibiting anthrax activity" would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's arguments were addressed in the response to the Final Office action. This rejection is maintained for reasons of record.

7. The rejection of claims 1, 3-8, 21 and 35-38 under 35 U.S.C. 102(b) as anticipated by Verma et al *(International Archives of Allergy and Immunology, 2000, 122:251-256)* is maintained for the reasons set forth on pages 12-15, paragraph 8 of the Final Office Action.

The rejection was on the grounds that Verma et al teach a 67kDa protein purified from *Imperata cylindrica* that binds IgE (page 252). Verma et al teach a protein that is stable at room temperature (page 252). Verma et al teach the 67-kDa protein is a cross-reactive allergen (see the Abstract). Verma et al teach that the 67-kDa protein has at least three antigenic determinants (see the Abstract). Claims limitations such as "hydrophobic in nature", "resistant to trypsin", "has no proteolytic activity", "inhibits proteolytic cleavage of protective antigen (PA) of *B. anthracis* in a dose dependent manner" and "is devoid of any carbohydrate moiety", wherein the range of about 25-20 ng completely inhibits the cleavage of the protective antigen of *B. anthracis* by trypsin" wherein protein in the range of about 15-5 ng completely inhibits the cleavage of the protective antigen of *B. anthracis* by trypsin", "wherein the protein in the range of about 25 ng to 11, 000 ng is effective in inhibiting the anthrax activity" and "wherein the protein in the range of about 50 to 10, 000 ng is effective in inhibiting anthrax activity" would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's arguments were addressed in the response to the Final Office action.

This rejection is maintained for reasons of record.

8. The rejection of claims 1, 3-8 ,21 and 35-38 under 35 U.S.C. 112, second paragraph is maintained for the reasons set forth on page 15, paragraph 9 of the Final Office Action.

The rejection was on the grounds that Claims 1, 3-8 and 21 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 in particular recites "...a 67-kDa protein isolated from "the genus related to *Imperata"*, "genus related to *Lolium"* , "a genus related to *Phleum"* and *"a* genus related to *Cynodon."* It is unclear as to what Applicant is referring. Clarification is required.

Applicant's arguments were addressed in the response to the Final Office action. This rejection is maintained for reasons of record.

9. The rejection of claims 1, 3-8, 21 and 35-38 under 35 U.S.C. 112, second paragraph is maintained for the reasons set forth on page 16, paragraph 10 of the Final Office Action.

The rejection was on the grounds that claims 1, 3-8 and 21 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 in particular recites "...partially inhibits..". It is unclear as to what Applicant is referring. Clarification is required.

This rejection is maintained for reasons of record.

Status of Claims

10. No claims are allowed.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vanessa L. Ford
Biotechnology Patent Examiner
August 1, 2007

ROBERT A. ZEMAN
PRIMARY EXAMINER